

## **Remarks**

### **Interview**

Applicants thank the Examiner for the personal interview on March 23, 2004 attended by Examiner Yang, Examiner Le, Dr. Brian Cunningham and Lisa Hillman. We discusses the differences between diffraction gratings and guided mode resonant filters.

### **The Office Action**

Pending claims 147-153 were not addressed on summary sheet of the Office Action. Applicants respectfully request correction.

### **Co-Pending Applications**

Applicants bring the following co-pending applications to the Office's attention: U.S. Ser. No. 09/929,957 filed 8/15/01; U.S. Ser. No. 09/930,352 filed 8/15/01; U.S. Ser. No. 10/415,037 filed 10/23/01; U.S. Ser. No. 10/399,940 filed 10/23/01 ; U.S. Ser. No. 10/059,060 filed 1/28/02; U.S. Ser. No. 10/058,626 filed 1/28/02; U.S. Ser. No. 10/201,818 filed 7/23/02; U.S. Ser. No. 10/237,641 filed 9/9/02; U.S. Ser. No. 10/201,878 filed 7/23/02; U.S. Ser. No. 10/227,908 filed 8/26/02; U.S. Ser. No. 10/233,730 filed 9/3/02; U.S. Ser. No. 10/180,374 filed 6/26/02; U.S. Ser. No. 10/180,647 filed 6/26/02; U.S. Ser. No. 10/253,846 filed 9/25/02; U.S. Ser. No. 10/196,058 filed 7/15/02; and U.S. Ser. No. 10/667,696 filed 9/22/03.

### **Information Disclosure Statements**

Information disclosure statements filed on the following dates have not been acknowledged by the Office: February 19, 2002, March 19, 2002, September 24, 2002, October 7, 2002, July 14, 2003, and October 10, 2003. Applicants have enclosed PTO

forms 1449 for these Information Disclosure Statements and respectfully request that signed copies be returned to the Applicants.

### **Clarification of the Specification**

Applicants wish to clarify the specification. The specification states that:

When the effective index of refraction of the grating region is greater than the substrate or the cover layer, a waveguide is created. When a filter is designed properly, incident light passes into the waveguide region and propagates as a leaky mode. A two-dimensional grating structure selectively couples light at a narrow band of wavelengths into the waveguide. The light propagates only a very short distance (on the order of 10-100 micrometers), undergoes scattering, and couples with the forward- and backward-propagating zeroth-order light. See page 29, line 20 through page 30, line 4.

However, Applicants have recently used techniques that provide for better resolution than were available to the Applicants at the time the application was filed and have determined that the biosensor structure is not accurately characterized as a waveguide because propagation of guided modes in the lateral direction are not supported. Rather, the guided mode resonant effect has been demonstrated to occur over a highly localized region of approximately 3 microns from the point that any photon enters the structure instead of the original determination of 10-100 micrometers.

### **Objections to the Claims**

Claims 51, 52, 59, and 67 stand as “objected to” for depending from non-elected claims. The claims have been amended and applicants respectfully request withdrawal of the objection.

Claim 101 stand as “objected to” as being in improper dependant form. Claim 101 has been amended to clarify that the claim is directed to a composition. Applicants respectfully request withdrawal of the objection.

## The Amendments

Claim 1 has been amended to state “a reflected radiation spectrum” and “a substrate. These amendments are made to clarify the antecedent basis for the claim terms and are not narrowing amendments.

Claims 1, 110, 114, 116, 129, 133, and 135 have been amended to clarify that the refractive index of the two-dimensional grating is greater than the refractive index fo the substrate. Support for the amendments can be found in the specification at, *inter alia*, page 29, lines 18 through page 30, line 8 (see also, “Clarification of the Specification” section above). These amendments do not narrow the claims and may even be considered to broaden the claims.

Claims 51, 52, 59, and 67 have been amended to remove dependencies to non-elected claims. This amendment is not a narrowing amendment and is made solely to remove mention to non-elected claims. Applicants reserve the right to prosecute the removed subject matter in a continuing application.

Claim 51 has been amended to eliminate the use of the term “second collection fiber probe.” This amendment is made solely for clarification and does not narrow the claim.

The Office Action asserts that claim 68 is indefinite and states that the claim is interpreted by the Office as “fabricated on the tip of the biosensor.” Applicants assert that the claim language as written is definite; however, in order to advance prosecution, the claim terminology has been amended to recite “fabricated on the tip of the biosensor.” Support for the amendment can be found in the specification at, *inter alia*, page 67, line

21 through page 68, line 1. This is not a narrowing amendment and is made merely to clarify what is claimed.

Claim 101 has been amended to clarify that the claim is a composition claim. The amendment does not narrow the claim and may broaden the claim.

**Rejection of claims 1-19, 60-65, 68, 69, 100, 101, 110-125, and 129-146 Under 35 U.S.C. §112, second paragraph**

Claims 1-19, 60-65, 68, 69, 100, 101, 110-125, and 129-146 stand rejected under 35 U.S.C. §112, second paragraph. Applicants respectfully traverse the rejection.

The Office asserts that claim 1 is definite for the use of the term “the reflected radiation spectrum.” Applicants believe that the term is indeed definite; however, in order to advance prosecution the term has been amended to recite “a reflected radiation spectrum.”

The Office asserts that claims 1, 110, 114, 116, 129, 133, and 135 are indefinite due to the use of the term “high.” These claims have been amended to clarify the language and are now definite.

The Office asserts that claims 2, 111, and 130 are indefinite due to the use of the terms “broad” and “narrow.” The claims recite biosensors or arrays of polynucleotides of the invention, wherein a narrow band of optical wavelengths is reflected from the biosensor or array when the biosensor or array is illuminated with a broad band of optical wavelengths. One of skill in the art, given the specification, would understand the meanings of broad band of optical wavelengths and narrow band of optical wavelengths as used in the claims.

For example, the specification teaches that “[i]n general, a biosensor of the invention will be illuminated with white light that will contain light of every polarization

angle.” See page 37, line 15-16. White light can be considered as containing a broad band of wavelengths in that it contains light from about 300 to about 900 nm. The examples in the application teach that the width (full-width at half-maximum (FWHM)) of the light reflected from the biosensor can be, for example, 1.5 nm (see example 3) or 0.25 nm (see example 4). While not in any way limiting the definition or interpretation of broad band of optical wavelengths and narrow band of optical wavelengths to these specific numbers and examples, one of skill in the art would understand from the specification that a biosensor of the invention can create a narrow optical resonant reflection that can be used to track with high sensitivity the interaction of biological materials, when light containing a broad band of optical wavelengths is used to illuminate the biosensor. See specification page 29, lines 1-6; and Examples 3, 4, and 6.

The Office asserts that claim 3 is indefinite due to the use of the term “the substrate.” Claim 1 has been amended so that claim 3 has proper antecedent basis for the use of the term “the substrate.”

The Office asserts that claim 13 is indefinite for the use of the term “the group.” The use of the language “selected from the group consisting of” is proper use of Markush language in a claim. See MPEP § 2173.05(h) (stating that “[a]lternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. One acceptable form of alternative expression, which is commonly referred to as a Markush group, recites members as being ‘selected from the group consisting of A, B and C.’ See *Ex parte Markush*, 1925 C.D. 126 (Comm’r Pat. 1925).”

The Office Action further asserts that claim 13 is indefinite for use of a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation in the same claim is considered indefinite. Claim 13 includes a Markush group that recites “selected from the group consisting of nucleic acids, polypeptides, antigens, polyclonal antibodies, monoclonal antibodies, single chain antibodies (scFv), F(ab) fragments, F(ab')<sub>2</sub> fragments, Fv fragments, small organic molecules, cells, viruses, bacteria, and biological samples.”

The MPEP states that:

The double inclusion of an element by members of a Markush group is not, in itself, sufficient basis for objection to or rejection of claims. Rather, the facts in each case must be evaluated to determine whether or not the multiple inclusion of one or more elements in a claim renders that claim indefinite. The mere fact that a compound may be embraced by more than one member of a Markush group recited in the claim does not necessarily render the scope of the claim unclear. For example, the Markush group, “selected from the group consisting of amino, halogen, nitro, chloro and alkyl” should be acceptable even though “halogen” is generic to “chloro.” See M.P.E.P. §2173.05(h)

Therefore, the Markush group recited in claim 13 is indeed definite and proper.

The Office Action asserts that claim 51 is indefinite for the use of the term “second collection fiber probe”. Claim 51 has been amended to eliminate the use of the term “second collection fiber probe.”

The Office Action asserts that claims 60-65 are indefinite for the use of the term “about.” The use of the term “about” in the instant claims is proper. The fact that claim language, including terms of degree, may not be precise, does not automatically render the claim indefinite under 35 U.S.C. §112, second paragraph. *Seattle Box Co., v. Industrial Crating & Packing, Inc.*, 731 F.2d 818, 221 U.S.P.Q. 568 (Fed. Cir. 1984).

Acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification. See M.P.E.P. § 2173.05(b). One of skill in the art would understand, in light of the specification, what is claimed.

The Office Action asserts that claim 68 is indefinite and states that the claim is interpreted by the Office as “fabricated on the tip of the biosensor.” Applicants assert that the claim language as written is definite; however, in order to advance prosecution, the claim terminology has been amended to recite “fabricated on the tip of the biosensor.” The Office Action asserts that claims 68 and 69 are indefinite because claim 68 recites the limitation of biosensors fabricated on the tip of the biosensor while claim 69 recites the limitation of having biosensors attached onto the tip of the probe. The Office Action asserts that the distinction between fabricating and attaching is not clear.

The specification teaches that:

A single biosensor element (comprising, for example, several hundred grating periods) can be fabricated into the tip of a fiber optic probe, or fabricated from a glass substrate and attached to the tip of a fiber optic probe. See page 67, line 21 through page 68, line 1.

Therefore, one of skill in the art would understand that one or more biosensors could be directly fabricated on the tip of a fiber optic probe or that one or more biosensors could be manufactured and then attached onto the tip of the probe. Therefore, claims 68 and 69 are definite.

The Office Action asserts that claim 101 is indefinite because the term “bottomless” could mean having no limitations or bounds or having no bottom. The determination of whether a claim is invalid as indefinite “depends on whether those

skilled in the art would understand the scope of the claim when the claim is read in light of the specification.” See *N. Am. Vaccine, Inc. v. Am. Cyanamid Co.*, 28 U.S.P.Q.2d 1333 (1993) (citation omitted). The specification clearly shows in Figure 10 that the term “bottomless” refers to a plate having no bottom. As such, one of skill in the art would understand the scope of the claim in light of the specification.

**Rejection of Claims 1-3, 5, 8-10, 12-16, 19, 100, 110-112, 114, 115, 117-119, 122, 129-131, 133, 134, 136, 138, 139, 140, and 143 Under 35 U.S.C. §102(b)**

Claims 1-3, 5, 8-10, 12-16, 19, 100, 110-112, 114, 115, 117-119, 122, 129-131, 133, 134, 136, 138, 139, 140, and 143 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Layton *et al.* U.S. Pat. No. 4,931,384 (the ‘384 patent). Applicants respectfully traverse the rejection.

Anticipation under 35 U.S.C. § 102 requires the presence in a single prior art disclosure of each and every element of a claimed invention. *Lewmar Marine Inc. v. Barient Inc.*, 3 USPQ2d 1766, 1767 (Fed. Cir. 1987).

The instant application claims a biosensor comprising a two-dimensional grating; a substrate that supports the two-dimensional grating, wherein the refractive index of the two-dimensional grating is higher than the refractive index of the substrate; and one or more specific binding substances immobilized on the surface of the two-dimensional grating opposite of the substrate layer. When the biosensor is illuminated a resonant grating effect is produced on a reflected radiation spectrum. The depth and period of the two-dimensional grating are less than the wavelength of the resonant grating effect.

The ‘384 patent does not teach or suggest a biosensor that produces a resonant grating effect on the reflected radiation spectrum when the biosensor is illuminated.



Rather, the '384 patent discloses a diffraction grating based biosensor. A diffraction grating based biosensor diffracts light into multiple orders. See e.g., Figure 1 and Col. 6, lines 4-10. The instantly claimed biosensors do not diffract light into multiple orders. The reason for this is that the dimensions of the biosensor (i.e., the period or pitch and height) are much smaller than the wavelength of the light that is incident upon it. Because of this, light is not diffracted, but passes through undisturbed – except for the resonant wavelength. The angle of the resonant wavelength light is not modified by the biosensor structure, as is required for a diffraction grating. The instantly claimed biosensors do not produce multiple orders of light that are diffracted in different directions. See e.g., specification page 30, line 9 through page 31, line 8.

Furthermore, the '384 patent does not teach or suggest a biosensor wherein the depth and period (pitch) of the two dimensional grating are less than the wavelength of the resonant grating effect. In one example, the '384 patent teaches a square profile (period =  $d$ , depth =  $h$ ) grating of a single refractive index ( $n$ ), and a single wavelength ( $W$ ), wherein zero order diffracted light will be suppressed when  $h=W/2(n-1)$ . First order diffraction will occur at angles  $\sin \theta = \pm W/d$ . Where the application is blood sampling  $d=6$  microns,  $W=550\text{nm}$ , and  $h=0.69$  microns. See Col. 4, lines 23-32. Therefore, the pitch is much greater than the wavelength, as required for diffraction orders in a diffraction grating. In the instantly claimed biosensor structure, the period is less than the resonant wavelength (sub-wavelength surface) so that a guided mode resonant effect is produced.

Additionally, the '384 patent teaches a “dip” in reflection as a function of incident angle of laser light. See e.g., Figure 4. The X axis is reflectivity and Y axis is angle of

incidence. See e.g., Col 5, line 58. Three profiles are shown in Figure 4, where the dip changes in magnitude and width.

In contrast, the instantly claimed biosensor produces a peak, rather than a dip, in the reflected radiation spectrum as a function of wavelength, rather than as a function of angle. The width and the magnitude of the resonant reflection peak is unchanged by the binding of cells or molecules to the biosensor surface. Only the wavelength of the reflected peak is changed in the instantly claimed biosensors. See e.g., page 63, line 1 through page 64, line 6; page 65, line 1-16. The '384 patent does not teach or suggest this resonant grating effect, but rather demonstrates a dip in reflection.

Finally, the Office Action asserts that a grating will inherently reflect a narrower band of optical wavelengths when illuminated with a band of optical wavelengths, as in any particular direction, only those waves of a given wavelength will be conserved, all the rest being destroyed because of interference with one another. See page 6, paragraph 21. The Office Action has not provided an art citation for this assertion. Applicants respectfully request that the Office provide documentary evidence or take official notice under M.P.E.P. §2144.03 for this assertion. Applicants believe that the above statement is erroneous. In fact, a diffraction grating, when illuminated at an angle with a range of incident wavelengths, will disperse each of the incident wavelengths at a different reflected or transmitted angle. The diffraction grating, therefore, can separate an optical beam containing many wavelengths into its individual wavelength components, but does not selectively transmit or reflect any one component.

In conclusion, the '384 patent does not teach each and every element of the claimed biosensors because the '384 does not teach, *inter alia*, a biosensor that produces

a resonant grating effect upon illumination and does not teach a two-dimensional grating with a depth and period that are less than the wavelength of a resonant grating effect. Applicants respectfully request withdrawal of the rejection.

**Rejection of Claim 11 Under 35 U.S.C. §103(a)**

Claim 11 stands rejected under 35 U.S.C. §103(a) as allegedly obvious over Layton *et al.* (the '384 patent). Applicants respectfully traverse the rejection.

Claim 11 recites a biosensor of claim 1 wherein the one or more specific binding substances are arranged in an array of distinct locations, wherein the distinct locations define a microarray spot of about 50-500 microns in diameter.

The Office Action asserts that the '384 patent teaches an array of distinct locations, but recognizes that the '384 patent does not teach or suggest distinct location defining microarray spots in the range of 50-500 microns in diameter. The Office Action asserts that it would have been obvious for one of skill in the art to use microarray spots in the range of 50-500 microns in diameter because it would take no more than routine experimentation for one of ordinary skill in the art to discover an optimum value of result effective variable.

Applicants disagree with the Office's assertions. However, as described above, the '384 patent does not teach or suggest a biosensor that produces a resonant grating effect upon illumination and does not teach a two-dimensional grating with a depth and period that are less than the wavelength of a resonant grating effect. Therefore, the '384 cannot render obvious claim 11. Applicants respectfully request withdrawal of the rejection.

**Rejection of Claims 120, 121, 141, and 142 Under 35 U.S.C. §103(a)**

Claims 120, 121, 141, and 142 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over the '384 patent and in view of Daniell (U.S. Pat. No. 6,587,276; "the '276 patent"). Applicants respectfully traverse the rejection.

The claims recite an array of polynucleotides that comprise an antireflective physical structure that is embossed into a surface of a substrate opposite of a two-dimensional grating. The antireflective physical structure can be a motheye structure. When the array of polynucleotides is illuminated a resonant grating effect is produced on the reflected radiation spectrum, wherein the depth and period of the two-dimensional grating are less than the resonant grating effect wavelength, and wherein the binding of a specific binding substance to the one or more types of polynucleotides attached at distinct locations to the two-dimensional grating produces a detectable change in the resonant grating effect on the reflected radiation spectrum.

The Office Action asserts that the '384 patent teaches a biosensor as discussed in paragraphs 18-31 of the Office Action. The Office Action recognizes that the '384 patent does not teach or suggest the use of anti-reflective "moth-eye" structures. The Office Action asserts that the '276 patent teaches optimized and economized performance by the use of hybrid refractive/diffractive surfaces and anti-reflective "moth-eye" structures.

Applicants submit that the Office Action has not established a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a

reasonable expectation of success. Finally, the references, when combined must teach or suggest all the claim limitations. See MPEP §2143.

Initially, the references do not teach all the claim limitations. As discussed above, the '384 patent does not teach or suggest a biosensor or an array of polynucleotides that produces a resonant grating effect upon illumination and does not teach a two-dimensional grating with a depth and period that are less than the wavelength of a resonant grating effect. Furthermore, the '384 patent does not teach or suggest that the binding of a specific binding substance to the one or more types of polynucleotides attached at distinct locations of the two-dimensional grating produces a detectable change in the resonant grating effect on the reflected radiation spectrum. The '276 patent does not teach or suggest these missing elements and the Office Action does not allege that these elements are taught by the '276 patent. Therefore, the cited references do not teach several elements of the claims.

Secondly, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. There must be some reason, suggestion, or motivation found in the cited references whereby a person of ordinary skill in the field of the invention would make the substitutions required. That knowledge cannot come from the applicants' disclosure of the invention itself. *Diversitech Corp. v. Century Steps, Inc.*, 7 U.S.P.Q.2d 1315,1318 (Fed. Cir. 1988); *In re Geiger*, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987); *Interconnect Planning Corp. v. Feil*, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985). The '384 patent teaches a diffraction grating based biosensor. The '276 patent teaches the use of motheye structures in a lens system based on total internal reflection that

reproduces three dimensional images. The '276 patent does not teach or suggest any type of biosensor or the use of an anti-reflective structure or a motheye structure in a biosensor. See "Summary of the Invention." Furthermore, the '276 patent does not teach any type of array of polynucleotides. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggest the desirability of the combination. See *In re Mills*, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990); MPEP §2143.01.

There is no suggestion or motivation to modify or combine the biosensor teachings of the '384 patent with components of the lens system of the '276 patent. The teachings of the two references are non-analogous and the structure and function of the two disclosures is very different.

Finally, there is no reasonable expectation of success in the combination of these two references. There is no alleged degree of predictability of success of combining an anti-reflective structure or motheye structure of a lens system that reproduces three dimensional images with a diffraction grating based biosensor.

Thus, claims 120, 121, 141, and 142 are not obvious over the '384 patent in view of the '276 patent because a *prima facie* case of obviousness has not been established. Applicants respectfully request withdrawal of the rejection.

**Rejection of Claims 6, 7, and 137 Under 35 U.S.C. §103 (a)**

Claims 6, 7, and 137 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over the '384 patent and in view of Rosenblatt (U.S. Pat. No. 5,337,183; the '183 patent). Applicants respectfully traverse the rejection.

Claims 6 and 7 recite the biosensor of claim 1 that further comprise a cover layer on the surface of the two-dimensional grating opposite of the substrate layer, wherein the one or more specific binding substances are immobilized on the surface of the cover layer opposite of the two-dimensional grating. According to claim 6 the cover layer comprises a material that has a lower refractive index than zinc sulfide, titanium dioxide, tantalum oxide, or silicon nitride. According to claim 7 the cover layer is glass, epoxy, or plastic. Claim 137 also recites a cover layer comprising a material selected from the group consisting of glass, epoxy and plastic.

The Office Action asserts that the '384 patent teaches the use of a biosensor comprising a grating with an aluminum oxide coating. The Office Action recognizes that the '384 patent does not teach the use of a cover layer. However, the Office Action asserts that the '183 patent teaches the use of a cover layer of sputtered glass or semiconductor to cover a grating to provide protection and modify the propagation characteristics of the plasmon. The Office Action concludes that it would have been obvious to use a cover layer to cover the grating of the '384 patent in order to provide protection and to modify the propagation characteristics of the plasmon.

Applicants submit that the Office Action has not established a *prima facie* case of obviousness. Initially, the references do not teach all the claim limitations. As discussed above, the '384 patent does not teach or suggest a biosensor that produces a resonant grating effect upon illumination and does not teach a two-dimensional grating with a depth and period that are less than the wavelength of a resonant grating effect. The '183 patent does not teach or suggest these missing elements and the Office Action does not

allege that these elements are taught by the '183 patent. Therefore, the cited references do not teach several elements of the claims.

Secondly, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. As discussed above, there must be some reason, suggestion, or motivation found in the cited references whereby a person of ordinary skill in the field of the invention would make the substitutions required.

The '384 patent teaches a diffraction grating based biosensor. The '183 patent teaches an optical device for the modulation of light transmission through the device by coupling or decoupling the radiation with a resonant mode of the device. See "Summary of the Invention." The '183 patent does not teach or suggest any type of biosensor. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggest the desirability of the combination. *See In re Mills*, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990); MPEP §2143.01.

There is no suggestion or motivation to modify or combine an optical device for modulation of light transmission as taught by the '183 patent with a diffraction grating-based biosensor of the '384 patent. The teachings of the two references are non-analogous and the structure and function of the two disclosures is very different.

Finally, there is no reasonable expectation of success in the combination of these two references. There is no alleged degree of predictability of success of combining a reference that teaches an optical device for the modulation of light transmission with a diffraction grating based biosensor.



Thus, claims 6, 7, and 137 are not obvious over the '384 patent in view of the '183 patent because a *prima facie* case of obviousness has not been established. Applicants respectfully request withdrawal of the rejection.

**Rejection of Claims 4, 113, 116, 132, and 135 Under 35 U.S.C. §103(a)**

Claims 4, 113, 116, 132, and 135 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over the '384 patent in view of Lenau. Applicants respectfully traverse the rejection.

The claims recite that a two-dimensional grating of a biosensor or array of polynucleotides is comprised of a material selected from the group consisting of zinc sulfide, titanium dioxide, tantalum oxide, and silicon nitride.

The Office Action asserts that the '384 patent teaches a grating comprised of an inorganic or a layer thereof and that Lenau teaches that silicon nitride is a dielectric material that is light, hard, resistant to corrosion and deformation. The Office Action concludes that it would have been obvious to have the two-dimensional grating of the '384 patent be comprised of silicon nitride as taught by Lenau since silicon nitride is a dielectric material that is light, hard, resistant to corrosion and deformation.

Applicants submit that the Office Action has not established a *prima facie* case of obviousness. Initially, the references do not teach all the claim limitations. As discussed above, the '384 patent does not teach or suggest a biosensor or an array of polynucleotides that produces a resonant grating effect upon illumination and does not teach a two-dimensional grating with a depth and period that are less than the wavelength of a resonant grating effect. Furthermore, the '384 patent does not teach or suggest that the binding of a specific binding substance to the one or more types of polynucleotides

attached at distinct locations to the two-dimensional grating produces a detectable change in the resonant grating effect on the reflected radiation spectrum. Additionally, as the Office Action recognizes, the '384 patent does not teach or suggest a two dimensional grating comprised of zinc sulfide, titanium dioxide, tantalum oxide and silicon nitride. Rather, the '384 patent teaches:

With such a structure, the plastics/metal interface may be planar, or it may conform to the surface structure of the metal layer itself. The metal used to form such layers may be gold, silver, copper or aluminum. Alternatively, the active surface of the substrate may be constituted by an inorganic oxide or a layer thereof. The inorganic oxide is advantageously an oxide of silver, copper or aluminum. Such an oxide layer may be produced by causing or allowing oxidation of the surface of a metal substrate or of a metal layer adhering to a substrate of a different material. See Col. 2, lines 46-58.

Lenau only teaches the properties of silicon nitride and does not teach or suggest the elements missing from the '384 patent. The Office Action does not allege that these other missing elements are taught by the Lenau. Therefore, the cited references do not teach several elements of the claims.

Secondly, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. As discussed above, there must be some reason, suggestion, or motivation found in the cited references whereby a person of ordinary skill in the field of the invention would make the substitutions required.

The '384 patent teaches a diffraction grating based biosensor. Lenau teaches the properties of silicon nitride. Lenau does not teach or suggest any type of biosensor. There is no suggestion or motivation to modify or combine the biosensor teachings of the

'384 patent with the silicon nitride teachings of Lenau. The teachings of the two references are non-analogous and the structure and function of the two disclosures is very different. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggest the desirability of the combination. *See In re Mills*, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990); MPEP §2143.01.

Finally, there is no reasonable expectation of success in the combination of these two references. There is no alleged degree of predictability of success of combining a reference that only teaches the properties of silicon nitride with a diffraction grating based biosensor.

Thus, claims 4, 113, 116, and 132-135 are not obvious over the '384 patent in view of the Lenau because a *prima facie* case of obviousness has not been established. Applicants respectfully request withdrawal of the rejection.

**Rejection of Claims 17, 18, and 66 Under 35 U.S.C. §103(a)**

Claims 17, 18, and 66 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Walt *et al.* (U.S. Pat. No. 6,377,721; the '721 patent) in view of the '384 patent. Applicants respectfully traverse the rejection.

Claims 17 and 18 recite a liquid-containing vessel comprising a biosensor of the invention as an internal surface. The vessel can be selected from the group consisting of a microtiter plate, a test tube, a petri dish and a microfluidic channel.

Claim 66 recites a biosensor composition comprising two or more biosensors of the invention wherein one or more specific binding substances are arranged in an array of distinct locations. The biosensors are associated with a holding fixture that holds each biosensor such that each biosensor can be placed into a separate well of a microtiter plate.

The Office Action asserts that the '721 patent teaches a biosensor comprising microwells formed at the distal end of individual fibers with a fiber optic array (microtiter plate).

Applicants submit that the Office Action has not established a *prima facie* case of obviousness. Initially, the references do not teach all the claim limitations. As discussed above, the '384 patent does not teach or suggest a biosensor that produces a resonant grating effect upon illumination and does not teach a two-dimensional grating with a depth and period that are less than the wavelength of a resonant grating effect. Furthermore, the '384 patent does not teach or suggest a liquid-containing vessel comprising a biosensor of the invention as an internal surface nor does the Office Action assert that the '384 patent teaches a liquid-containing vessel. Additionally, the '384 patent does not teach or suggest a biosensor composition comprising two or more biosensors of the invention wherein one or more specific binding substances are arranged in an array of distinct locations and wherein the biosensors are associated with a holding fixture that holds each biosensor such that each biosensor can be placed into a separate well of a microtiter plate, nor does the Office Action assert that the '384 patent teaches these elements. The '721 patent does not teach or suggest the elements missing from the '384 patent. Therefore, cited references do not teach several elements of the claims.

Secondly, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. As discussed above, there must be some reason, suggestion, or motivation found in the cited references whereby a person of ordinary skill in the field of the invention would make the substitutions required.

The '384 patent teaches a diffraction grating based biosensor. The '721 patent teaches biosensors made up of microwells that are etched into the ends of optical fibers. See Col. 6, line 42 through Col. 7, line 5. The '721 patent does not teach or suggest label-free grating-based biosensors. Rather, the '721 patent teach non-grating based biosensors that rely upon labels such as fluorophores, chromophores, chemiluminescence or bioluminescence. See e.g., Col. 18, line 11 through Col. 30. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggest the desirability of the combination. *See In re Mills*, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990); MPEP §2143.01.

There is no suggestion or motivation to modify or combine that the microwells, which are used in a non-grating based biosensor that requires that use of labels for detection, as disclosed in the '721 patent with the label-free, diffraction grating based biosensor of the '384 patent. The teachings of the two references are non-analogous and the structure and function of the two disclosures is very different.

Additionally, there is no teaching or suggestion in the '721 patent of a biosensor composition comprising two or more biosensors of the invention wherein one or more specific binding substances are arranged in an array of distinct locations, and wherein the biosensors are associated with a holding fixture that holds each biosensor such that each biosensor can be placed into a separate well of a microtiter plate. Nor does the Office Action assert that there is such a teaching in the '721 patent.

Finally, there is no reasonable expectation of success in the combination of these two references. There is no alleged degree of predictability of success of combining a

reference that teaches non-grating based biosensors made up of microwells that are etched into the ends of optical fibers with a diffraction grating based biosensor.

Thus, claims 17, 18, and 66 are not obvious over the '384 patent in view of the '721 patent because a *prima facie* case of obviousness has not been established.

Applicants respectfully request withdrawal of the rejection.

**Rejection of Claims 17, 18, 51, 52, 59, 66-69, 101, 123-125, and 144-146 Under 35 U.S.C. §103(a)**

Claims 17, 18, 51, 52, 59, 66-69, 101, 123-125, and 144-146 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Pinkel *et al.* (U.S. 6,146,593; "the '593 patent") in view of the '384 patent. Applicants respectfully traverse the rejection.

***Claims 17, 18, and 101***

Claims 17 and 18 recite a liquid-containing vessel comprising a biosensor of the invention as an internal surface. The vessel can be selected from the group consisting of a microtiter plate, a test tube, a petri dish and a microfluidic channel. Claim 101 recites that a biosensor of the invention is attached to a bottomless microtiter plate.

The Office Action asserts that the '593 patent teaches a microtiter plate with sensors attached at the bottom (Fig. 4) and the use of the biosensor in a comparative genomic hybridization process. The Office Action recognizes that the '593 patent does not teach or suggest a biosensor with a two-dimensional grating, wherein when the biosensor is illuminated a resonant grating effect is produced on the reflected radiation spectrum. The Office Action, however, alleges that the '384 patent teaches such a biosensor and that it would have been obvious to use the biosensor of the '384 patent in

the system of the '593 patent in order to enable quantitative detection of specific antigens as an aid to diagnosis.

Applicants submit that the Office Action has not established a *prima facie* case of obviousness. Initially, the references do not teach all the claim limitations. As discussed above the '384 patent does not teach or suggest a biosensor or an array of polynucleotides that produces a resonant grating effect upon illumination and does not teach a two-dimensional grating with a depth and period that are less than the wavelength of a resonant grating effect. Furthermore, the '384 patent does not teach or suggest that the binding of a specific binding substance to the one or more types of polynucleotides attached at distinct locations to the two-dimensional grating produces a detectable change in the resonant grating effect on the reflected radiation spectrum. Additionally, the '384 patent does not teach or suggest a liquid-containing vessel comprising a biosensor of the invention as an internal surface and the '384 patent does not teach or suggest a biosensor of the invention that is attached to a bottomless microtiter plate.

The '593 patent teaches optical fiber based biosensors that do not comprise a grating and that require that the biological species to be detected are labeled with a fluorescent, luminescent, or colorimetric label to produce a detectable optical signal. See Col. 13, lines 51-53. The elements missing from the '384 patent are not taught by the '593 patent. Additionally, contrary to the Office Action's allegation, the '593 patent does not teach or suggest patent a microtiter plate with sensors attached at the bottom in Fig. 4. See Col. 5, lines 54-61 and Col. 7, lines 22-35. Therefore, the cited references do not teach several elements of the claims.

Secondly, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. As discussed above, there must be some reason, suggestion, or motivation found in the cited references whereby a person of ordinary skill in the field of the invention would make the substitutions required.

The '384 patent teaches a diffraction grating based biosensor. The '593 patent teaches optical fiber based biosensors that do not comprise a grating and that require that the biological species to be detected are labeled with a fluorescent, luminescent, or colorimetric label to produce a detectable optical signal. There is no suggestion or motivation to modify or combine the biosensor teachings of the '384 patent with the teachings of the '593 patent. The teachings of the two references are non-analogous and the structure and function of the two disclosures is very different. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggest the desirability of the combination. *See In re Mills*, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990); MPEP §2143.01.

Finally, there is no reasonable expectation of success in the combination of these two references. There is no alleged degree of predictability of success of combining an label-free diffraction grating based biosensor with an optical fiber based biosensor that requires labels.

Thus, claims 17, 18 and 101 are not obvious over the '384 patent in view of the '593 patent because a *prima facie* case of obviousness has not been established. Applicants respectfully request withdrawal of the rejection.

***Claims 51, 52, 123-125, and 144-146***



Claim 51 recites a detection system comprising a biosensor of the invention, a light source that directs light at the biosensor, and a detector that detects light reflected from the biosensor. A first fiber probe, which is an illuminating fiber probe, having two ends is connected at its first end to the detector. A second fiber probe, which is a collection fiber probe, having two ends, is connected at its first end to the light source. The first and second fiber probes are connected at their second ends to a third fiber probe. The third fiber probe acts as an illumination and collection fiber probe. The third fiber probe is oriented at a normal angle of incidence to the biosensor and supports counter-propagating illuminating and reflecting optical signals.

Claim 52 recites a detection system comprising a biosensor of the invention, a light source that directs light at the biosensor, and a detector that detects light reflected from the biosensor. An illuminating fiber probe is connected to the light source and is oriented at a 90 degree angle to a collecting fiber probe. The collecting fiber probe is connected to the detector. Light is directed through the illuminating fiber probe into a beam splitter that directs the light to the biosensor, wherein reflected light is directed into the beam splitter that directs the light into the collecting fiber.

Claims 123 and 144 recite a detection system comprising a fiber probe comprising one or more illuminating optical fibers that are connected at a first end to a light source, and one or more collecting optical fibers connected at a first end to a detector. The second ends of the illuminating and collecting fibers are arranged in line with a collimating lens that focuses light onto an array of polynucleotides of the invention. According to claims 124 and 145, the illuminating fiber and the collecting fiber are the

same fiber. According to claims 125 and 146, the light source illuminates the array of polynucleotides from its top surface or from its bottom surface.

The Office Action asserts that '593 patent teaches the claimed detection system and that the '384 patent teaches the biosensor component of the claimed detection system despite the fact that the Office Action recognizes in Paragraph 48 of the Office Action that "the '384 and the '593 patents do not teach or suggest a detection system comprised to a first fiber probe connected to a detector and a second fiber probe connected to a light source and both connected to a third fiber probe."

Applicants submit that the Office Action has not established a *prima facie* case of obviousness. Initially, the references do not teach all the claim limitations. As discussed above, the '384 patent does not teach or suggest a biosensor or an array of polynucleotides that produces a resonant grating effect upon illumination and does not teach a two-dimensional grating with a depth and period that are less than the wavelength of a resonant grating effect. Furthermore, the '384 patent does not teach or suggest that the binding of a specific binding substance to the one or more types of polynucleotides attached at distinct locations to the two-dimensional grating produces a detectable change in the resonant grating effect on the reflected radiation spectrum. Additionally, the '384 patent does not teach or suggest the claimed detection system.

The '593 patent teaches optical fiber based biosensors that do not comprise a grating and that require that the biological species to be detected are labeled with a fluorescent, luminescent, or colorimetric label to produce a detectable optical signal. See Col. 13, lines 51-53. The Office Action does not allege that the elements missing from

the '384 patent are taught by the '593 patent. Therefore, the cited references do not teach several elements of the claims.

Secondly, as discussed above, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or to combine the teachings of the '384 patent with the '593 patent.

Finally, as discussed above, there is no reasonable expectation of success in the combination of the '384 patent with the '593 patent.

Thus, claims 51, 52, 123-125, and 144-146 are not obvious over the '384 patent in view of the '593 because a *prima facie* case of obviousness has not been established. Applicants respectfully request withdrawal of the rejection.

#### ***Claims 67-69***

Claim 67 recites a biosensor composition comprising one or more biosensors of the invention on a tip of a multi-fiber optic probe. Claim 68 recites a biosensor composition, wherein one or more biosensors of the invention are fabricated on the tip of multi-fiber optic probe. According to claim 69, the one or more biosensors are attached onto the tip of the probe.

The Office Action asserts that '593 patent teaches the claimed biosensor composition and that the '384 patent teaches the biosensor component of the claimed biosensor composition. Applicants submit that the Office Action has not established a *prima facie* case of obviousness. Initially, the references do not teach all the claim limitations. As discussed above, the '384 patent does not teach or suggest a biosensor or an array of polynucleotides that produces a resonant grating effect upon illumination and does not teach a two-dimensional grating with a depth and period that are less than the

wavelength of a resonant grating effect. Furthermore, the '384 patent does not teach or suggest that the binding of a specific binding substance to the one or more types of polynucleotides attached at distinct locations to the two-dimensional grating produces a detectable change in the resonant grating effect on the reflected radiation spectrum.

The Office Action does not allege that the elements missing from the '384 patent are taught by the '593 patent. Therefore, the cited references do not teach several elements of the claims.

Secondly, as discussed above, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or to combine the teachings of the '384 patent with the '593 patent.

Finally, as discussed above, there is no reasonable expectation of success in the combination of the '384 patent with the '593 patent. There is no alleged degree of predictability of success of combining a label-free grating based biosensor with an optical fiber based biosensor that requires labels.

Thus, claims 67-69 are not obvious over the '384 patent in view of the '593 because a *prima facie* case of obviousness has not been established. Applicants respectfully request withdrawal of the rejection.

#### ***Claims 59 and 66***

Claim 59 recites a biosensor composition comprising two or more biosensors of the invention, wherein the biosensors are associated with a holding fixture. According to claim 66, the holding fixture holds each biosensor such that each biosensor can be placed into a separate well of a microtiter plate.

The Office Action asserts that '593 patent teaches the claimed biosensor composition and that the '384 patent teaches the biosensor component of the claimed biosensor composition. Applicants submit that the Office Action has not established a *prima facie* case of obviousness. Initially, the references do not teach all the claim limitations. As discussed above, the '384 patent does not teach or suggest a biosensor or an array of polynucleotides that produces a resonant grating effect upon illumination and does not teach a two-dimensional grating with a depth and period that are less than the wavelength of a resonant grating effect. Furthermore, the '384 patent does not teach or suggest that the binding of a specific binding substance to the one or more types of polynucleotides attached at distinct locations to the two-dimensional grating produces a detectable change in the resonant grating effect on the reflected radiation spectrum. Additionally, the '384 patent does not teach or suggest the claimed biosensor system.

The Office Action does not allege that the elements missing from the '384 patent are taught by the '593 patent. Therefore, the cited references do not teach several elements of the claims.

Secondly, as discussed above, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or to combine the teachings of the '384 patent with the '593 patent.

Finally, as discussed above, there is no reasonable expectation of success in the combination of the '384 patent with the '593 patent.

Thus, claims 59 and 66 are not obvious over the '384 patent in view of the '593 because a *prima facie* case of obviousness has not been established. Applicants respectfully request withdrawal of the rejection.

### **Rejection of Claims 60-63 Under 35 U.S.C. §103(a)**

Claims 60-63 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over the '593 patent in view of the '384 patent. Applicants respectfully traverse the rejection.

Claim 60 recites a biosensor composition comprising about 50 to about 1,000 individual biosensors of the invention, wherein the biosensors are associated with a holding fixture. According to claim number 61, the composition comprises about 96 biosensors. According to claim 62, the composition comprises about 384 biosensors. According to claim 63, the two or more biosensors each comprise about 25 to about 1,000 distinct locations.

The Office Action asserts that the biosensor composition of the '384 patent and the '593 patent as discussed above do not teach or suggest the specific feature of 50-1,000 individual biosensors. However, the Office Action concludes that no more than routine experimentation would be required to discover an optimum value of a result effective variable.

Applicants submit that the Office Action has not established a *prima facie* case of obviousness. Initially, the references do not teach all the claim limitations. As discussed above the '384 patent does not teach or suggest a biosensor or an array of polynucleotides that produces a resonant grating effect upon illumination and does not teach a two-dimensional grating with a depth and period that are less than the wavelength of a resonant grating effect. Furthermore, the '384 patent does not teach or suggest that the binding of a specific binding substance to the one or more types of polynucleotides attached at distinct locations to the two-dimensional grating produces a detectable change

in the resonant grating effect on the reflected radiation spectrum. Additionally, the '384 patent does not teach or suggest the claimed biosensor compositions.

The Office Action does not allege that the elements missing from the '384 patent are taught by the '593 patent. Therefore, the cited references do not teach several elements of the claims.

Secondly, as discussed above, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or to combine the teachings of the '384 patent with the '593 patent.

Finally, as discussed above, there is no reasonable expectation of success in the combination of these two references.

Thus, claims 60-63 are not obvious over the '384 patent in view of the '593 because a *prima facie* case of obviousness has not been established. Applicants respectfully request withdrawal of the rejection.

**Rejection of Claims 64-65 Under 35 U.S.C. §103(a)**

Claims 64-65 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over the '593 patent in view of the '384 patent. Applicants respectfully traverse the rejection.

Claim 64 recites a biosensor composition comprising two or more biosensors of the invention, wherein the biosensors are associated with a holding fixture and wherein each biosensor is about 1 mm<sup>2</sup> to about 5 mm<sup>2</sup>. According to claim 65 each biosensor is about 3 mm<sup>2</sup>.

The Office Action asserts that the biosensor composition of the '384 patent and the '593 patent as discussed above, do not teach or suggest the specific feature of each biosensor being about 1 mm<sup>2</sup> to about 5 mm<sup>2</sup>. However, the Office Action concludes

that no more than routine experimentation would be required to discover an optimum value of a result effective variable.

Applicants submit that the Office Action has not established a *prima facie* case of obviousness. Initially, the references do not teach all the claim limitations. As discussed above the '384 patent does not teach or suggest a biosensor or an array of polynucleotides that produces a resonant grating effect upon illumination and does not teach a two-dimensional grating with a depth and period that are less than the wavelength of a resonant grating effect. Furthermore, the '384 patent does not teach or suggest that the binding of a specific binding substance to the one or more types of polynucleotides attached at distinct locations to the two-dimensional grating produces a detectable change in the resonant grating effect on the reflected radiation spectrum. Additionally, the '384 patent does not teach or suggest the claimed biosensor compositions.

The Office Action does not allege that the elements missing from the '384 patent are taught by the '593 patent. Therefore, the cited references do not teach several elements of the claims.

Secondly, as discussed above, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or to combine the teachings of the '384 patent and the '593 patent.

Finally, as discussed above, there is no reasonable expectation of success in the combination of the '384 patent with the '593 patent.

Thus, claims 64-65 are not obvious over the '384 patent in view of the '593 because a *prima facie* case of obviousness has not been established. Applicants respectfully request withdrawal of the rejection.



### **Rejection of Claim 51 Under 35 U.S.C. §103(a)**

Claims 51 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over the '593 patent and the '384 patent and further in view of Saaki *et al.* (U.S. Pat. No. 5,606,170; the '170 patent). Applicants respectfully traverse the rejection.

Claim 51 recites a detection system comprising a biosensor of the invention, a light source that directs light at the biosensor, and a detector that detects light reflected from the biosensor. A first fiber probe, which is an illuminating fiber probe, having two ends is connected at its first end to the detector. A second fiber probe, which is a collection fiber probe, having two ends is connected at its first end to the light source. The first and second fiber probes are connected at their second ends to a third fiber probe. The third fiber probe acts as an illumination and collection fiber probe. The third fiber probe is oriented at a normal angle of incidence to the biosensor and supports counter-propagating illuminating and reflecting optical signals.

The Office Action asserts that the '384 and the '593 patents do not teach or suggest a detection system comprised to a first fiber probe connected to a detector and a second fiber probe connected to a light sources and both connected to a third fiber probe. However, the Office Action asserts that the '170 patent teaches these elements.

Applicants submit that the Office Action has not established a *prima facie* case of obviousness. Initially, the references do not teach all the claim limitations. As discussed above, the '384 patent does not teach or suggest a biosensor or an array of polynucleotides that produces a resonant grating effect upon illumination and does not teach a two-dimensional grating with a depth and period that are less than the wavelength of a resonant grating effect. Furthermore, the '384 patent does not teach or suggest that

the binding of a specific binding substance to the one or more types of polynucleotides attached at distinct locations to the two-dimensional grating produces a detectable change in the resonant grating effect on the reflected radiation spectrum. Additionally, the '384 patent does not teach or suggest the claimed detection system.

The '593 patent teaches optical fiber based biosensors that do not comprise a grating and that require that the biological species to be detected are labeled with a fluorescent, luminescent, or colorimetric label to produce a detectable optical signal. See Col. 13, lines 51-53. The '170 patent teaches a non-grating based detection system that requires species to be labeled with a fluorescent tag to produce a detectable optical signal. See Col. 22, line 56 through Col. 24, line 12. The Office Action does not allege that the elements missing from the '384 patent are taught by the '593 patent or the '170 patent. Therefore, the cited references do not teach several elements of the claims.

Secondly, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. As discussed above, there must be some reason, suggestion, or motivation found in the cited references whereby a person of ordinary skill in the field of the invention would make the substitutions required.

The '384 patent teaches a diffraction grating based biosensor. The '593 patent teaches optical fiber based biosensors that do not comprise a grating and that require that the biological species to be detected are labeled with a fluorescent, luminescent, or colorimetric label to produce a detectable optical signal. The '170 patent teaches a non-grating based detection system that requires species to be labeled with a fluorescent tag to produce a detectable optical signal. There is no suggestion or motivation to modify or

combine the biosensor teachings of the '384 patent with the teachings of the '593 patent and the '170 patent. The teachings of the three references are non-analogous and the structure and function of the three disclosures are very different. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggest the desirability of the combination. *See In re Mills*, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990); MPEP §2143.01.

Finally, there is no reasonable expectation of success in the combination of these three references. There is no alleged degree of predictability of success of combining a label-free grating based biosensor with sensors that require labels.

Thus, claim 51 is not obvious over the '384 patent in view of the '593 patent and the '170 patent because a *prima facie* case of obviousness has not been established. Applicants respectfully request withdrawal of the rejection.

**Rejection of Claims 71, 72, and 74 Under 35 U.S.C. §103(a)**

Claims 71, 72, and 74 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Goodman *et al.* (U.S. Pat. No. 6,316,153; the '153 patent) in view of the '384 patent. Applicants respectfully traverse the rejection.

Claims 71 recites a detection system comprising a biosensor of claim 1; a laser source that directs a laser beam to a scanning mirror device, wherein the scanning mirror device is used to vary the laser beam's incident angle; an optical system for maintaining collimation of the incident laser beam; and a light detector. Claim 72 recites that the scanning mirror device is a linear galvanometer. Claim 74 recites that the laser is a diode laser with a wavelength selected from the group consisting of 780 nm, 785 nm, 810 nm, and 830 nm.

The Office Action asserts that the '153 patent teaches a laser source, an optical system, a galvanometer and light detector. The Office Action furthermore asserts that the '384 patent teaches a biosensor and that the use of selectively coated two-dimensional gratings would enable quantitative detection of specific antigens as an aid in diagnosis. The Office Action concludes that it would have been obvious to use the biosensor taught by the '384 patent in the detection system of the '153 patent to enable quantitative detection of specific antigens as an aid in diagnosis.

Applicants submit that the Office Action has not established a *prima facie* case of obviousness. Initially, the references do not teach all the claim limitations. As discussed above, the '384 patent does not teach or suggest a biosensor that produces a resonant grating effect upon illumination and does not teach a two-dimensional grating with a depth and period that are less than the wavelength of a resonant grating effect. The '153 patent does not teach or suggest the elements missing from the '384 patent. Therefore, the cited references do not teach or suggest several elements of the claims.

Secondly, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. As discussed above, there must be some reason, suggestion, or motivation found in the cited references whereby a person of ordinary skill in the field of the invention would make the substitutions required.

The '384 patent teaches a diffraction grating based biosensor. The '153 patent teaches modified laser scanning confocal microscope that is used to fabricate microstructures. See Col. 19, lines 1-21. The '153 patent does not teach or suggest any type of detection system that could be used with a two-dimensional grating based

biosensor. There is no suggestion or motivation to modify or combine the biosensor teachings of the '384 patent with the confocal microscope of the '153 patent. The teachings of the two references are non-analogous and the structure and function of the two disclosures is very different. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggest the desirability of the combination. *See In re Mills*, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990); MPEP §2143.01.

Finally, there is no reasonable expectation of success in the combination of these two references. There is no alleged degree of predictability of success of combining modified laser scanning confocal microscope that is used to fabricate microstructures with a diffraction grating based biosensor.

Thus, claims 71, 72, and 74 are not obvious over the '384 patent in view of the '153 patent because a *prima facie* case of obviousness has not been established. Applicants respectfully request withdrawal of the rejection.

#### **Rejection of Claim 73 Under 35 U.S.C. §103(a)**

Claim 73 stands rejected under 35 U.S.C. §103(a) as allegedly obvious over the '153 patent and the '384 patent. Applicants respectfully traverse the rejection.

Claim 73 recites the detection system of claim 71 wherein the linear galvanometer operates at a frequency of about 2 Hz to about 120 Hz and a mechanical scan angle of about 10 degrees to about 20 degrees. The Office Action asserts that while the detection system of the '153 patent and the '384 patent do not recite the specific feature of a galvanometer with a mechanical scan angle in the range of 10-20 degrees, it would have been obvious for a person of ordinary skill of the art to use a mechanical scan angle in the

range of 10-20 degrees, because no more than routine experimentation would be necessary to discover an optimum value of a result effective variable.

Applicants submit that the Office Action has not established a *prima facie* case of obviousness. Initially, the references do not teach all the claim limitations. As discussed above, the '384 patent does not teach or suggest a biosensor that produces a resonant grating effect upon illumination and does not teach a two-dimensional grating with a depth and period that are less than the wavelength of a resonant grating effect. The '153 patent does not teach or suggest the elements missing from the '384 patent. Therefore, the cited references do not teach or suggest several elements of the claims.

Secondly, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. As discussed above, there must be some reason, suggestion, or motivation found in the cited references whereby a person of ordinary skill in the field of the invention would make the substitutions required.

The '384 patent teaches a diffraction grating based biosensor. The '153 patent teaches modified laser scanning confocal microscope that is used to fabricate microstructures. See Col. 19, lines 1-21. The '153 patent does not teach or suggest any type of detection system that could be used with a two-dimensional grating based biosensor. There is no suggestion or motivation to modify or combine the biosensor teachings of the '384 patent with the confocal microscope of the '153 patent. The teachings of the two references are non-analogous and the structure and function of the two disclosures is very different. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also

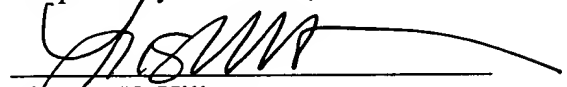
suggest the desirability of the combination. *See In re Mills*, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990); MPEP §2143.01.

Finally, there is no reasonable expectation of success in the combination of these two references. There is no alleged degree of predictability of success of combining modified laser scanning confocal microscope that is used to fabricate microstructures with a diffraction grating based biosensor.

Thus, claim 73 is not obvious over the '384 patent in view of the '153 patent because a *prima facie* case of obviousness has not been established. Applicants respectfully request withdrawal of the rejection.

Date: 4-6-04

Respectfully submitted,



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